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10/589,181	06/04/2007	Rijkje Cornelia Sprong	0470-062372	5882

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,181	SPRONG ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-46* is/are pending in the application.

4a) Of the above claim(s) *31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *29-46* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 29–46 are pending. Claims 31–41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 08/24/2009.

Maintained formal matters, objections, and/or rejections:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30 and 42–46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou (Exp Biol Med (Maywood). 2002 Mar;227(3):214-22) in view of Mallee (U. S. Publication No. 20020090670).

In addition:

The steps outlined in claim 42 for obtaining the mixture of peptides are identical to the steps for preparing Mallee's mixture of peptides. See Mallee, Abstract.

The molecular weight of the peptides in Mallee's preparation is preferably between 200 Da and 8000 Da, more preferably between 1000 Da and 5000 Da (Mallee, paragraph [0002]).

In a very special embodiment, the protein source comprises whey protein isolates (WPI) and/or whey protein concentrates (WPC). See Mallee, paragraph [0029].

Preferably, the steps are done at conditions, wherein sulfur bridges between cysteine residues as present in the proteins in the protein source are kept in the oxidized form as much as possible. In this way, cysteine-rich peptide mixtures are obtained, in which most of the cysteine residues are oxidized and coupled to other peptides through disulfide bridges. See Mallee, paragraph [0032].

It is preferred to carry out the hydrolytic processes in acidic environments. At acid pH the disulfide bridges in cystine are more stable than at basic pH. See Mallee, paragraph [0034].

The preparations comprise cysteine-rich peptides, comprising 7-20 w/w % cysteine. See Mallee, paragraph [0037].

In summary, the mixture of peptides used in the claimed method is produced by a process that is identical or substantially identical to the process used to prepare Mallee's composition. Therefore, with respect to the newly added limitation in claim 29 and newly added claims 43–46 a prima facie case of obviousness has been established.

The invention is prima facie obvious over the prior art.

Response to Arguments

Applicants argue that:

> Zhou did not investigate orally administering MT. Zhou suggests that increasing antioxidant defense is a potential therapy for alcoholic liver disease ....

> … Zhou … concludes that supplementation with antioxidants as protection against alcohol liver injury has been widely investigated, but that no antioxidant has been advised for clinical treatment. (Zhou, page 221). Hence, there is no general motivation to use antioxidants for such treatment. On the contrary, the art as such teaches away from using common antioxidants in treating alcohol-induced injury.

Applicants' arguments have been fully considered but they are not persuasive. The examiner does not agree with applicants' conclusion that the art teaches away from using antioxidants in treating alcohol-induced liver injury because Zhou teaches: 1) antioxidants are likely potential pharmaceutical agents for the treatment of alcoholic liver disease (Abstract); 2) increasing hepatic antioxidant defense is likely a potential therapy for alcoholic liver disease (page 214, right column, full paragraph 3); 3) most studies have suggested that supplementing antioxidants could suppress ethanol-induced liver injury (page 221, right column, last paragraph); and 4) developing antioxidant therapy is an important strategy to improve the prevention and treatment of alcoholic liver injury (page 221, right column, last paragraph). Based on these teachings the examiner concludes that neither the prior in general nor Zhou in particular teaches away from using antioxidants, be they common or uncommon, in treating alcohol-induced injury.

Applicants argue that:

> Zhou then continues by concluding, based on their studies, that MT, i.e. not antioxidants in general, may be useful in such treatment. MT (metallothionein) is a group of proteins which is very high in cysteine: about a third (33%) of their amino acids (Zhou, page 215). MT contains some 50-70 amino acids, and thus has a molar weight in the range of 6,000-8,000. The cysteine residues in MT will be in their reduced form, since it is produced in the mouse body and Zhou stresses the antioxidant (= reducing) activity of MT.

> The results obtained by Zhou provide no indication that replacing MT-transgenic with other proteinaceous material, which is (orally) administered, and which has a much lower cysteine content, wherein the cysteines are in the oxidized form, as required by the claimed invention would be effective in a similar treatment.
>
> The peptides to be used in the instant invention - as distinct from the protein of Zhou, are administered, i.e., exposed to the (food) processing and digestive conditions, and not produced by the body itself. They are a mixture of peptides derived from common proteins, especially whey proteins, and are significantly shorter (300-6,000, especially 400-5,000 kDa) than MT. They have a lower cysteine contant (6.5-20%, typically around 7-7.5 %, as compared to some 33% for the MT), and most importantly, are in the oxidized form. This means that the thiol groups of the cysteine residue (-SH), have been oxidized to produce disulfide links (-S-S-) between couples of cysteine residues, and the peptides have lost most of their (direct) reducing power. In view of the teaching of Zhou, no effect from such oxidized, i.e., not reducing, not directly anti-oxidative peptides could be expected. Examples 8 and 10 provide evidence that the claimed invention has the desired effect.

Applicants' arguments have been fully considered but they are not persuasive. Applicants' argument regarding the differences between MT and the composition administered in the claimed method may in itself be valid, but does not address the issue in question.

The examiner does not believe that it is a question of substituting Mallee's preparation for Zhou's MT. Rather the issue is whether Zhou provides some teaching, suggestion or motivation to use Mallee's preparation in the treatment of alcoholic liver disease.

Zhou teaches:

1) oxidative stress plays an important etiologic role in the development of alcoholic liver disease. See page 214, right column, full paragraph 2.

2) One of the most prominent defense systems in the liver is the presence of reduced glutathione (GSH).

3) Most studies have reported that acute ethanol administration decreases hepatic GSH content. See page 214, right column, full paragraph 3.

4) The decrease in GSH has been related to an enhanced oxidation of GSH to oxidized glutathione (GSSG) as a consequence of increased generation of reactive oxygen species. See page 214, right column, full paragraph 3.

5) Restoration of GSH has been shown to inhibit ethanol-induced liver injury. See page 214, right column, full paragraph 3.

6) These results suggest that increasing hepatic antioxidant defense is likely a potential therapy for alcoholic liver disease. See page 214, right column, full paragraph 3.

Mallee teaches: 1) a preparation comprising cysteine-rich peptides, comprising 7-20 w/w % cysteine (claim 16) and 2) its use in a medicament for the treatment of conditions mediated by oxidative damage (claim 20) and 3) for the elevation of cellular glutathion levels in the human or animal body (claim 21); 4) Glutathion is therefore regarded as an important compound against oxidative stress related diseases (paragraph [0004]).

It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to restore GSH to inhibit ethanol-induced liver injury, as taught by Zhou, and to modify that teaching by administering a preparation comprising cysteine-rich peptides, comprising 7-20 w/w % cysteine, as taught by Mallee, in order to prevent and/or reduce effects of alcohol consumption with a reasonable expectation of success.

One of ordinary skill in the art would be motivated to make this modification because there is increasing evidence that oxidative stress plays an important etiologic role in the development of alcoholic liver disease, acute ethanol administration decreases hepatic GSH content, restoration of GSH has been shown to inhibit ethanol-induced liver injury, glutathion is regarded as an important compound against oxidative stress related diseases, a preparation comprising cysteine-rich peptides, comprising 7-20 w/w % cysteine treats conditions mediated by oxidative damage and elevates cellular glutathion levels.

Applicants argue that:

> According to the Office Action, Mallee teaches a preparation comprising cysteine-rich peptides, comprising 7-20 w/w% cysteine. However, Mallee does not provide any motivation to one of ordinary skill in the art to modify the teachings of Zhou (i.e., MT-transgenic) to incorporate the preparation of Mallee to teach the claimed method. Specifically, neither Mallee nor Zhou, either alone or in combination, teach or suggest the claimed method for restoring thiol homeostasis in a subject in need thereof, comprising administering to said subject an effective amount of a mixture of peptides comprising at least 6.5 % wt cysteine, wherein at least 80% of the cysteine residues are in the oxidized form.

Applicants' arguments have been fully considered but they are not persuasive. Zhou teaches: 1) oxidative stress plays an important etiologic role in the development of alcoholic liver disease (page 214, right column, full paragraph 2); 2) ethanol administration decreases hepatic GSH content (page 214, right column, full paragraph 3); and 3) restoration of GSH has been shown to inhibit ethanol-induced liver injury (page 214, right column, full paragraph 3). Mallee provides a preparation comprising cysteine-rich peptides, comprising 7-20 w/w % cysteine (claim 16) that is useful for the treatment of conditions mediated by oxidative damage (claim 20) and that elevates

cellular glutathion levels in the human or animal body (claim 21). One of ordinary skill in the art would be motivated to use Mallee's preparation for the treatment of ethanol-induced liver injury because one of ordinary skill in the art would have a reasonable expectation that the elevation of cellular glutathion levels would inhibit ethanol-induced liver injury.

New Formal Matters, Objections and/or Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of "6.5 wt." (claim 42) are not clearly set forth.

Claim 44 depends from a canceled claim, and thus makes no sense, since it is incomplete. The metes and bounds are not clearly set forth. In the interest of compact prosecution the claim will be interpreted as incorporating the limitations of claim 29. However, this interpretation of the claim does not relieve applicant from the requirement to respond to the instant rejection.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY NICKOL, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-0835.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM.

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
MAY 19, 2010